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Interstitial Cystitis

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EDWARD O. JANOSKO, II

1974

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INTERSTITIAL CYSTITIS

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Part I

Review of the Literature

History of Terminology

Interstitial cystitis, also referred to as "Hunner's ulcer (99)," is an uncommon lesion of the urinary bladder which was first described as a clinical entity in this country by Guy Hunner in 1914 as a "rare type of bladder ulcer (75)." He reported in detail eight cases which were characterized by suprapubic pain, urinary frequency, sterile urine, and ulceration of the vertex of the bladder seen at cystoscopy. Previous to this, however, in 1907 Nitze in Germany described an inflammation of the bladder which extended into the submucosa. This lesion was accompanied by suprapubic pain, and the mucosa was seen at cystoscopy to crack on distending the bladder. He called this "cystitis parenchymatosa (130)." The same condition was also described by Knorr in 1908 (95). The identification of this clinical entity has been attributed to Mercier, Tait, and Skene (113), but this is probably incorrect. Mercier in 1836 described perforating ulcerations in the bladder secondary to chronic infective cystitis (123). Tait described four cases of chronic cystitis which were relieved symptomatically by the creation of a vesico-vaginal fistula to drain the bladder (174). These cases were not characteristic of interstitial cystitis and probably represented infective cystitis: one case of dysuria with albuminuria and alkaline urine, and another with spontaneous perforation of a bladder neck ulcer. Skene, who first used the term "Interstitial Cystitis," almost certainly described an infective process.

> The redness of acute inflammation gradually gives way to a muddy gray color, the membrane being smeared in places with a dark yellow mucopurulent secretion. As the disease advances, there is excessive cell growth on the free mucous surface. Patches of ulceration appear here and there attended with the formation of pus and occasional hemorrhage. . .

> In advanced cases with deep ulceration, the muscular fibres, (which resist the destructive process longest) are occasionally seen, stretching from one side of an ulcer to the other, forming a sort of a bridge. . . In some cases salts of the urine are deposited. When the disease has destroyed the mucous membrane partially or wholly, and extends to the muscular parietes, we have what is known as Interstitial Cystitis; and if the serous coat becomes involved we also have pericystitis.
>
> Perforation of the peritoneum sometimes occurs, allowing infiltration of urine. This usually develops general Peritonitis or Septicemia (or both) and death almost inevitably follows (161).

The condition described by Mercier, Tate, and later Fenwick was similar to that described by Skene and was not interstitial cystitis as pointed out by Hunner in his original observations: "I am confident that I am presenting for your consideration a group of cases of simple ulcer of the bladder differing in many respects from the Fenwick type ulcer (75)."

Since Hunner's original description, a number of terms have been used to describe this condition. Cullen named it "elusive ulcer," a term later adopted by Hunner (72), because of the difficulty in visualizing the lesion (27). Geraghty suggested the term "paracystitis" since the inflammation frequently involved the paravesical tissues (58). He also called it "localized cystitis" since only a portion of the bladder seemed to be involved. Reed used the term "punctate ulcer," while Keene preferred "circumscribed panmural ulcerative cystitis" to describe the thickening of the entire bladder wall associated with minute ulcerations of the mucosa (145,90). It was known as "submucous ulcer" at the Mayo Clinic because it was felt that the process involved primarily the submucosa (13). "Linear ulcer (67)," "panmural fibrosis (25)," "submucous cystitis (34)," "panmural cystitis (9),"

"submucous fibrosis (54)," "cystitis lymphopathia (143)," "cystitis infiltrans circumscripta (136)," and "bladder fissure (68)" have all been used. Until 1949 new synonyms were being coined (143). Peterson encouraged the acceptance of the term "interstitial cystitis" although it was first used by Skene to describe a bacterial cystitis (136, 161).

Kinder and Smith (98) in 1958 reported an incidence for interstitial cystitis of 0.15% for all urological admissions to St. Peter's Hospital in London over a ten year period. Bowers and Lattimer (9) reported a 0.07% incidence in the same population in this country. In first visit urology patients Von Garrelts (56) reported a 0.24% to 0.29% incidence, while Peterson and Hager (136) reported a 0.47% rate. Hand (65) reported the highest incidence rate in the literature for this same group at 4.79%, but this has not been the common experience. Peterson (136) reported a 1.9% incidence in adult females with urologic problems, and Bowers and Lattimer (9) reported a 2.1% incidence in all patients with cystitis.

In the pediatric population (1-12 yrs.), Geist and Antolak (57) reported a 4.8% incidence in their urological patients, while Chenoweth (20) reported a 1.1% rate in this group. Other papers report a surprisingly high incidence rate of interstitial cystitis in children. McDonald (116) reported a 12.1% incidence in children with bladder dysfunction and Geist (57) reported an incidence of 14.3% in children with voiding difficulty and sterile urine. These high incidences can be explained by pre-selection as only those children with bladder dysfunction and sterile urine were included.

Interstitial cystitis is not a common disease occurring in about 1-3/1,000 urologic hospital admissions which comprise 10% of all hospital admissions.

The disease most frequently affects middle aged females (20,57,116,61), but has been observed in men (13,63,164), children (116,20,57), and the elderly (61). The average age in a combined series was forty-seven (68,75,166,

70,186,132,93,180). The female to male ratio has been reported to be 5.6:1.0 in a collected series of 1365 cases previously reported in the literature (9). This ratio is not a true representative figure since cases in men are more frequently reported than in women. The ratio of 11:1 reported by a single investigator, with the largest series of over 400 patients, is probably more accurate (65).

The geographic distribution of this disease has not been studied, but Somerset (168) states that interstitial cystitis is more common in the United States than in Australia or Britain, and Shipton (157) states that it is rare in Europe.

Many attempts have been made to correlate interstitial cystitis with other disorders because of its unknown etiology. Rheumatoid arthritis (132,158), thyroiditis (158), chronic granulomatous disease (94), polyarteritis (132), idiopathic muscle fibrosis (187), vaginitis, purpura, colitis, hypertension, sprue, cholecystitis, pelvic inflammatory disease (9), endometriosis (181), lupus erythematosus (60), tonsillitis (78), oral infection (122), and urethritis (79) have all been reported in association with interstitial cystitis, but none has occurred with sufficient frequency to suggest any causal relationship.

Presently there appear to be only two associated disorders: allergy and carcinoma of the bladder arising from the site of a Hunner ulcer. The incidence of a previous history of allergic disorders in patients with interstitial cystitis is greater than expected in the normal population as reported by Hand (65), Higgins (70), and Oravisto (132) with respective incidences of 14.7%, 19%, and 13%. Carcinoma of the bladder arising from a Hunner's ulcer was first reported by Hagner in 1937 (62).

Previous to this Hunner had only one similar experience (81). Later Rusche and Hager (151) reported two cases, one with carcinoma occurring six months after diagnosis of interstitial cystitis, and the other three years after diagnosis. Vose and Dixey (176) reported two cases, one with carcinoma at the initial diagnosis of interstitial cystitis, and the other three years after diagnosis. Bumpus and Barrington (62) also reported one case each. Of the total nine cases, the diagnosis of interstitial cystitis was made by cystoscopy with initial biopsies obtained only in three cases. Kinder (93) in 1958 reported the misdiagnosis of interstitial cystitis for carcinoma of the bladder in one case out of forty-two. And Badenoch (2) reported two patients with carcinoma of the bladder who were referred to him for management of their interstitial cystitis. Smith and Badenoch (167) reported three cases of carcinoma of the bladder originally diagnosed as interstitial cystitis, and Cristol (26) reported two similar cases. In review, except for the two cases of carcinoma occurring three years after the initial diagnosis, all other cases can be attributed to an error in diagnosis. Whether the actual two cases of carcinoma did arise from the Hunner's ulcer and were causally related can not be ascertained. The available data does not allow for a comparison between the incidence of carcinoma of the bladder in patients with interstitial cystitis and the incidence of carcinoma of the bladder in the general population.

The onset of interstitial cystitis is usually insidious, but may follow an episode of acute cystitis (113,155). The most common symptom is "clocklike" frequency and nocturia occurring as often as every fifteen minutes during the day and hourly at night (55,93). Often this is associated with urgency. There is usually a persistent, knife-like suprapubic pain which is increased with bladder distention, aggravated by sitting, movement, and menstruation, and alleviated by bladder emptying (155,2,136). The patient may often place her finger over the exact spot of the lesion (155). Rarely the pain is located in the right or left quadrant and may simulate appendicitis. In females, the pain may radiate to the rectum, vagina, thigh, hip, or buttocks. In males, the pain radiates to the penis and increases with micturition (63). Dyspareunia, perineal and back pain, and urinary retention are less common; intermittent hematuria, most often encountered when the urine is self contained too long, dysuria, and burning on urination occasionally occur (155). The systemic manifestations are rare and include weight loss, weakness, lassitude, and anorexia (38). A combined series illustrates the incidence of the various symptoms in decreasing order of frequency (65,166,38,100, 69): frequency 92%, nocturia 78%, dysuria 62%, suprapubic bladder pain 33%, urgency 21%, intermittent hematuria 20%, burning 19%, back pain 11%, incontinence 6%, and retention 2%.

The physical examination usually reveals only suprapubic tenderness and tenderness over the base of the bladder on pelvic examination (2).

The urine is usually clear, but microscopic examination reveals a few red and white cells per high power field in approximately 90% of patients (38,70,100, 162,146,3). The culture of the urine is usually sterile, but 50% of cases will have positive cultures from a complicating episode of bacterial infection during the course of the disease (75,132,38,165). Urography reveals a normal genito-urinary tract in most cases, unless there is a decrease in bladder capacity or complicating hydroureter due to vesico-ureteral reflux or secondary obstruction from fibrosis. The bladder emptying is normal (2) and cystometric studies are not helpful (149).

The differential diagnosis of interstitial cystitis must include: chronic infective cystitis, tuberculosis, carcinoma of the bladder (especially in males), radiation cystitis, bilharzia, pyogenic simple ulcers, syphilis, amebic cystitis, bladder neck obstruction, fibrotic contracted bladder secondary to gonorrheal infection, granular urethritis, lymphogranuloma venereum, and the psychosomatic cystitis syndrome (2,41,24,65,93,133,161).

There are numerous descriptions of the pathology of interstitial cystitis in the literature (25,47,58,65,68,69,75,78,90,95,113,130,136,159,166,168,184, 187). The disease has been divided into three stages based on the cystoscopic, macroscopic, and microscopic appearances of the lesion (43,65,120). Stage I requires the presence of an ulceration, stage II is characterized by ulceration and fibrosis, and stage III represents a markedly contracted fibrotic bladder.

Stage I

The cystoscopic feature shows that the ulcers or fissures are usually discrete in the early stage and every centimeter of the bladder must be inspected (78). At the site of a visible lesion the mucosa is pale (78,120) and is surrounded by a salmon pink area of congestion interspersed with dilated capillaries in an irregular pattern. When these areas are touched with an instrument or overdistended they characteristically bleed and readily manifest the typical appearance of the stellate ulcer (75,78). The suprapubic pain which the patient experiences may be reproduced (68). Overdistention of the bladder also produces numerous fissures with sharp edges approximately 0.5 mm by 2.0 mm at the sites of increased vascularity which ooze droplets of blood (75,78,90,68,120). These early lesions may be overlooked with inadequate filling and led Young to recommend double distention of the bladder (68,187). The fissure with bleeding is one of the characteristic findings in interstitial cystitis. The areas of mucosal pallor may be caused from previous ulceration and scarring (154,68). Except for the area(s) of involvement, the mucosa appears

normal. The apex of the bladder is most often involved, while the ureteral orifices and trigone are usually spared. In a combined series of sixty-six cases the ulcers were distributed in the following manner: apex 35%, right wall 16.5%, posterior wall 16.5%, anterior wall 12%, left wall 11%, and trigone 9% (78,98,166,136, 13,122). Hand reported a 38% incidence of trigonal ulcers, a finding not subsequently substantiated (65,18,83,168). Typically only one area is involved, although 30% of cases have multiple ulcerations. The bladder capacity is normal or only slightly reduced at this stage (65,78).

Descriptions of the gross pathology of case studies of interstitial cystitis are limited since the disease is uncommon, and specimens are obtainable only at autopsy or operation; there has been only one case report at necropsy (154) and operative intervention is presently rare. The best descriptions are contained in early publications when excision of the ulcer was the therapy of choice (58,75,90,98). However, stage I lesions are not described.

The microscopic appearance of the bladder in interstitial cystitis shows a chronic inflammatory process involving all layers of the bladder. The appearance is very similar to chronic cystitis except for the additional fibrosis of the submucosa (70). The histologic examination reveals that the entire bladder is involved regardless of the position of the ulcer as demonstrated by multiple random bladder biopsies in contrast to the macroscopic and cystoscopic findings of discrete lesions (132).

The mucosa in the involved area shows an atrophied and flattened epithelium (68), with occasional thickening secondary to squamous metaplasia, hornification, or goblet cell proliferation (78,184). The epithelium may be thinned or cuboidal in areas of healed ulcers or where dense subepithelial deposits raise the mucosa (68,70). At the edge of an active ulcer, the epithelium ends abruptly with a precipitous edge, or there may be a single layer of cuboidal cells attempting to bridge the ulcer gap (78). At the base of the ulcers there are red blood cells or granulation tissue rich in capillaries with a preponderance of connective tissue infiltrated by leukocytes and round cells, depending on the age of the lesion (78,90). The basement membrane which is locally thickened is discontinuous at the edge of the ulcer (78).

The submucosa is markedly thickened due to edema, cellular infiltration, and fibrosis. The degree of edema may be disproportional to the amount of inflammation as compared to that seen in simple ulceration of the bladder (166). The cellular infiltrate is predominantly lymphocytic. Plasma cells, monocytes, granulocytes, histiocytes, and mast cells may also be present (78,166). There may be a follicular arrangement of lymphocytes and plasma cells with a scattered infiltration of eosinophils in some cases (184). Connective tissue is increased and related to the duration of the lesion (166). The lymph spaces are distended with lymphocytes and granulocytes and the arteriolar walls may show thickening. Rarely a perivascular infiltrate of leukocytes is present without arteriolar necrosis (65).

The veins and capillaries are dilated with a modest accumulation of leukocytes. Although these changes are diffuse, there is a tendency to focal prominence especially around nerve trunks (166).

The muscularis is usually edematous throughout with lymphocytes and plasma cells interspersed between muscle fibers, focally prominent at nerve trunks (166). Mast cells, as demonstrated by Leder stain, are found scattered throughout (166,160). The amount of fibrosis is proportional to the duration and stage of the lesion and to the degree of inflammation. Early edema and inflammation is generally replaced by fibrosis, and the late stage resembles "linitis plastica of the non-neoplastic type (26,159,137)."

The peritoneum and paravesical tissues may be thickened with round cell infiltrate or fibrosis (78,65,166), especially in the area of a large ulcer (58). The adjacent perivesical fat may contain a round cell infiltrate (52). Bohm and Franksson have reported round cell infiltration of sacral nerve roots with myelin sheath degeneration, but this has not been confirmed (52,53,121).

Stage II

The cystoscopic appearance of this stage shows more areas of involvement, larger ulcerations and longer fissures up to 7.0 mm (65,68,90). Fibrous tissue is more prolific with pale raised bands stretching across the bladder wall. The bladder capacity is markedly reduced to within 150 cc (65).

Macroscopically, the bladder appears to be involved only in the areas of ulceration. Here the entire bladder wall and the peritoneum is thickened. The inflammatory process may extend to involve the paravesical tissues and adhesions between the bladder and paravesical tissues have been noted (90,68). There is contracture of the bladder with cicatrization.

The microscopic appearance is as in stage I with the additional characteristic of an increase in fibrous tissue.

Stage III

Stage III represents "the end-stage bladder." The markedly reduced bladder capacity of less than 150 cc. may make the cystoscopic examination difficult. The amount of scar tissue is significantly increased over the earlier stages. The raised ridges or bands of fibrous tissue criss cross from one side of the bladder to the other (65,68,120) and form a stellate pattern (47,155). There is little or no edema and the organ takes on the character of a "leather bag" with no distensibility and much rigidity (155).

Macroscopically the bladder is small and the entire bladder wall is thickened and fibrotic (90). The paravesical involvement may be substantial with occasional obstruction of the ureters. Hydroureter may be due to obstruction, but more often is due to reflux.

The microscopic feature of this stage is an increase in fibrosis and decrease in edema.

The pathogenesis of interstitial cystitis is of unknown etiology. It is a chronic inflammatory process affecting the entire bladder wall without evidence of a preceding acute or subacute process. It may be progressive and followed by healing with cicatrization, undergo spontaneous remission, or arrest.

The etiology of interstitial cystitis remains obscure. The theories that have been proposed have little conclusive evidence to substantiate them. The principal theories of etiology can be classified as infectious, vascular, lymphatic, neurogenic, and immunologic.

Hunner in 1915 first postulated an infectious origin suggesting that a distant suppurative focus with hematogenous spread of organisms incited a chronic infection of the bladder wall (76,80). This was based on a previous work (77) in which he claimed to have demonstrated a causal relationship, albeit invalid, between tonsillitis and granular urethritis, and a finding that all of his patients with interstitial cystitis had chronic urethritis. Bumpus insisted that as the bladder wall and not the mucosa was mainly affected, the infection could not be transmitted by the urine, but must be from a hematogenous spread (13). Rosenow was unable to detect any localization in the bladder wall when organisms isolated from infected tonsils were injected intravenously in rabbits and dogs (150), but LeFur (122) was able to produce ulceration in the bladder, though not typical of interstitial cystitis, by injecting non-specific organisms intravenously into rabbits and simultaneously injuring the bladder wall. Bumpus (122) supported this concept by demonstrating submucosal and mucosal hemorrhage in the bladders of rabbits injected with alpha streptococci from periapical tooth infections in patients with interstitial cystitis. Similar lesions however were found in the gallbladder, stomach, and kidneys. There has been no other work which has supported the idea of an etiology due to a focus of infection.

Interstitial cystitis has also been thought to occur from bladder wall infection secondary to local spread of pelvic infection via lymphatics or following pelvic surgery. Winsbury-White in 1933 injected India ink into the cervix of guinea pigs and demonstrated ink particles in the bladder lymphatics and produced inflammatory changes in the bladder following the injection of Mycobacteria tuberculosis into the cervix of guinea pigs (186). Others have attributed the cystitis to lymphogranuloma venereum (24,112) and Neisseria gonorrhea (41).

The evidence for an infective etiology is inconclusive. Many patients have no focus of infection, and neither the removal of such foci, nor the use of antibiotics have altered the course of the disease (91,52). Keene (91) and Kretchmer (98) were unable to detect any pelvic infections in their series of thirty-four patients with interstitial cystitis. McCrea in 1962 was unable to reproduce the lesion with group C streptococci injected directly into the bladder wall even with lymphatic obstruction of the bladder (114). Smith was unable to culture any organisms from the bladder wall macerated in culture medium (165). Recently Hanash and Pool cultured the urine and bladder wall biopsies of thirty patients with interstitial cystitis for viruses, bacteria, and fungi, all of which were sterile (64). This study has apparently ended a controversy.

Keene suggested that the lesion of interstitial cystitis was secondary to a paracystitis (90). Herbst in 1937 induced a paracystitis in female dogs by implanting an infected bone spicule in a pouch created between the posterior bladder wall and the uterus (68). All dogs had a decreased bladder capacity and mucosal hemorrhages

were produced after prolonged bladder distention; however, the cystoscopic lesions were not typical of interstitial cystitis and histologic examination showed only chronic inflammatory changes in the area of the adhesions. A severe paracystitis is uncommon in patients with the disease and occurs only in severe cases.

The theory of lymphatic obstruction in the bladder wall was proposed by Powell in 1945, who was impressed by the similarity of the microscopic appearance of interstitial cystitis and chronic lymphedema (142). He postulated that obstruction of lymphatic flow: by infection as a result of pelvic inflammatory disease, cervicitis, urethritis or proctitis; by mass obstruction by fibroids; or by surgical interruption of lymphatics caused edema of the bladder wall. The edema was felt to reduce blood flow, lower tissue oxygenation, and cause nerve irritability which induced frequency of urination further impairing lymphatic flow. The edema would ultimately result in fibrous proliferation. He obstructed lymphatic flow from the bladder in dogs by intralymphatic injection of thorotrast which produced edema and fibrosis, but there was no cellular infiltrate. It is of interest that enterocystoplasty increased lymphatic flow via neocollateralization, but does not ameliorate the course of the disease (114).

Vascular insufficiency of the bladder has been suggested as a possible cause of the disease by Engel on the basis that a few cases were found to have a decrease in capillary vascularity in the fundus (43). Herbst ligated the posterior vessels to the bladder in two dogs, but failed to produce the cystoscopic and histologic changes of interstitial cystitis (68). Vascular narrowing or obstruction has not been observed in

interstitial cystitis and enterocystoplasty, which increases the blood supply to the bladder, does not prevent progression of the disease (114).

Hand in 1949 suggested a neurologic mechanism because of the prominence of focal inflammation around nerve bundles which has been described elsewhere (65, 165). Bohm and Franksson (53) reported endoneural and perineural fibrosis with myelin sheath degeneration and round cell infiltration in rhizotomy specimens of the sacral nerves from patients with severe interstitial cystitis, but there were no adequate controls and this finding has not been confirmed (121). Bladder capacity increases in patients with interstitial cystitis following sacral neurectomy, evidence which has been used to suggest a neurogenic component (126,135,185). Sacral neurectomy however has a similar effect on the normal bladder. A lesion of the bladder consisting of edema, round cell infiltration of the lamina propria and submucous fibrosis without gross ulceration of the bladder wall has been produced in monkeys by application of aluminum gel or lycopodium spores to the sacral nerve roots (121). These observations have not been followed up.

More recently immunologic mechanisms have been invoked as a cause of interstitial cystitis. Fister drew attention to the similarity of the lesions in interstitial cystitis and lupus erythematosus and suggested a common etiology (47). Both diseases are uncommon, usually occur in females, exhibit a chronic course, and have the histopathologic characteristics of edema, round cell infiltration and fibrosis. Lupus is now considered to be an auto-immune disease. Shipton also regarded interstitial cystitis as a manifestation of a collagen disease and cited four cases associated with

lupus erythematosus and scleroderma (157). Attempts have been made to detect antibodies to bladder tissue in patients with chronic interstitial cystitis using fluorescent antibody techniques. Silk (158) in 1970 claimed to have demonstrated anti-bladder antibodies in the serum of nine of twenty patients with interstitial cystitis employing an indirect Coons method and that these antibodies could not be detected in normal patients, in those with chronic bacterial cystitis, or in patients with known anti-thyroid and anti-gastric antibodies. He incubated the patient's serum with normal human bladder tissue and then incubated the bladder tissue with fluoroscein labeled rabbit anti-human globulin antibody. This indirect Coons method is not always reliable since non-specific reactions may occur. Silk did not demonstrate tissue specificity since no other tissues were incubated with the serum as controls. The specificity of a reaction should be determined by absorption of the antibody with non-bladder antigens prior to incubation with the target cells.

Gordon et al. (60) reported the presence of IgA, IgM, and IgG in the muscle or submucosa in the bladders of five of eight patients with interstitial cystitis. They used the direct Coons method incubating fluorescein labeled rabbit anti-human IgA, IgG, and IgM with sections of bladder from patients with interstitial cystitis. Three of four patients with other bladder diseases however exhibited the presence of IgG and IgM in the submucosa. No normal bladders were studied. They also found that five of five patients with interstitial cystitis had anti-bladder antibodies in their sera as shown by the indirect Coons method when their own bladders were used as the target antigen. Both controls with other bladder diseases also exhibited this phenomenon.

The pooled sera of five normal patients did not exhibit any evidence for the presence of antibody when tested against the same bladder tissue. Again the specificity of the reaction was not determined as other tissues were not used as controls. Furthermore, in only two patients was the indirect Coons method positive when the direct Coons was negative. In the other three patients the direct Coons was initially positive, thus the indirect Coons was necessarily positive. He also demonstrated lymphocytotoxic antibody in one patient and anti-nuclear factor in two others, one of which also exhibited the LE phenomenon. He postulated an antigen in the bladder was released or altered and induced an immune response in the susceptible host which would initiate and perpetuate an inflammatory process in the bladder, a conclusion for which there seems to be insufficient evidence.

Jokinen in 1970 (84) was unable to confirm Silk's findings of the presence of anti-bladder antibodies in the serum of patients with interstitial cystitis. He used a similar method; namely, incubation of the patient's serum with normal bladder tissue prior to incubation with fluorescein labeled rabbit anti-human gamma globulin antibody; however, he absorbed the test sera with lyophilized rat kidney, liver, and homogenates of human uterine muscle to remove non-specific antibodies. This method could conceivably have also removed the specific bladder antibodies which might cross react with the antigens used for absorption. He subsequently was unable to detect any specific immunoglobulin in the bladder basement membrane of patients with interstitial cystitis using the direct Coons method (85), however, the fluorescein labeled anti-human gamma globulin was absorbed with acetonized rat liver particles

prior to testing which may explain why he was unable to confirm Gordon's findings. It is of interest that patients with discoid lupus erythematosus were found to have immunoglobulins present in the bladder basement membrane. Oravisto et al. demontrated the presence of anti-nuclear antibodies in titers of greater than 1:10 in 28 of 33 patients with interstitial cystitis in the absence of a positive LE phenomenon (132). They later reported an 85% incidence of anti-nuclear antibodies in patients with interstitial cystitis compared with a 6% incidence in a control group matched for sex and age (84). Antibodies to smooth muscle, mitochondria, thyroid tissue, and cell nuclei were found in 94% of cases, but these were also present to the same degree in the control group.

The response to steroid therapy, which has been suggested as indicating autoimmune disease (118) has been variable and inconclusive in patients with interstitial cystitis (2,32,182). This may suggest that the bladder changes may not be due to an immune process.

The treatment of patients with interstitial cystitis is unsatisfactory in many cases as the etiology remains obscure. However, many modes of therapy have been used with varying degrees of success in producing relief of symptoms. Sometimes remissions may be induced and occasionally the process is arrested though probably this is due to the self limitation of the disease.

Almost all the empirical treatments developed have been abandoned, and only a few are currently employed. Therapy can be divided into surgical and non-surgical and following is a tabulation of the methods that have been used.

Surgical Therapy

Local Excision

1) Extraperitoneal segmental excision of the ulcer (75, Hunner, 1914).
2) Simple cystotomy (58, Geraghty, 1917).
3) Transperitoneal resection of the ulcer (145, Reed, 1919).
4) Wide excision of the ulcer (66, Herbst, 1920).
5) Subtotal cystectomy (48, Folsom et al., 1940).
6) Ileocystotomy (46, Ferris, 1955).
7) Sigmoidocystoplasty (56, von Garrelts, 1966).
8) Caecocystoplasty (56, von Garrelts, 1966).

Open Fulguration

1) Open gauze curettage of the ulcer (145, Reed, 1919).
2) Fulguration of the ulcer through the open bladder (100, Furniss, (1926).

Transurethral resection and fulguration

1) Cystoscopic division of the fibrous bands in the bladder wall (155, Seaman, 1950).

2) Transurethral resection of the urethra and removal of Skene's ducts with cauterization (146, Riba, 1958).

3) Application of silver nitrate to the ulceration (75, Hunner, 1914).

4) Electrocauterization of the ulcer area (75, Hunner, 1919).

5) Application of the silver stick to the ulcer (75, Hunner, 1914).

6) Diathermy fulguration of the ulcer (101, Kreutzmann, 1922).

7) Shortwave diathermy fulguration (4, Barnes, 1947).

Neurectomy

1) Resection of the presacral nerve (144, Quinby, 1931).

2) Resection of the presacral nerve and division of the paravertebral chains and sacral rami communicantes (104, Learmonth, 1931).

3) Presacral neurectomy and sacral ganglionectomy (135, Pearl, 1938).

4) Anterolateral chordotomy (129, Nesbit, 1947).

5) Differential sacral neurectomy (127, Moulder and Meirowsky, 1956).

Urinary Diversion

1) Bilateral ureterosigmoidostomy in two separate stages (23, Cousellor, 1937).

2) Bilateral simultaneous ureterosigmoidostomy (110, Lower and Schlumberger, 1939).

3) Ileal loop conduit applied to interstitial cystitis (11, Bricker, 1950; 2, Badenoch, 1971).

Bladder Distention and Urethral Dilatation

1) Distention of the bladder by the method of Young (75, Hunner, 1914).

2) Dilatation of urethral strictures and ureteral strictures (79, Hunner, 1920).

3) Overdistention of the bladder (99, Frontz, 1922), popularized by Bumpus (15, Bumpus, 1930).

4) Self distention of the bladder by delaying micturition, (144, Quinby, 1931), popularized by Ormond (133, Ormond, 1935).

5) Gradual prolonged bladder distention by means of a balloon catheter (89, Kearns, 1932).

6) Mechanical periodic bladder distention and irrigation by means of tidal irrigation (107, Longacre, 1936).

7) Distention of the bladder by means of a condom (8, Bohne and Fetz, 1954).

8) Distention of the bladder with Chlorpactin WCS-90, monoxy-chlorosene (131, O'Conor, 1955).

Bladder Instillation

1) Intravesical instillation of bichloride of mercury (75, Hunner, 1914).

2) Intravesical instillation of gomenol oil (75, Hunner, 1914).

3) Intravesical instillation of boric acid (75, Hunner, 1914).

4) Intravesical instillation of Thompson fluid (75, Hunner, 1914).

5) Intravesical instillation of silver iodide (90, Keene, 1920).

6) Intravesical instillation of argyrol (170, Stevens, 1923).

7) Intravesical instillation of acriflavine and mercurochrome (91, Braasch, 1925).

8) Intravesical instillation of silver nitrate in increasing concentrations (33, Dodson, 1926).

9) Application of pure phenol (156, Sears, 1935).

10) Intravesical instillation of triphenylmethane (30, Davis, 1941).

11) Intravesical instillation of amniotin oil (39, Eikner, 1942).

12) Intravesical instillation of histamine and hyaluronidase (143, Powell, 1949).

13) Intravesical instillation of cajaput oil (3, Baker and Callahan, 1959).

14) Intravesical instillation of iodophor (181, Warres , 1962).

15) Intravesical instillation of dimethyl sulfoxide, DMSO (172, Stewart et al., 1968).

Bladder Injection

1) Transurethral injection of absolute alcohol into the submucosa in and around the ulcer (1, Alexander, 1936).

2) Transurethral infiltration of adrenalin and procaine into the ulcer (149, Rose, 1951).

3) Transurethral injection of hydrocortone hyaluronidase into the submucosa and muscularis around the ulcer (153, Schulte and Reynolds, 1956).

4) Local hydrocortisone for Hunner's ulcer (183, Johnstone, 1956).

Oral and Parenteral Medication

1) Removal of allergic foods and adrenalin by intramuscular injection (37, Duke, 1922).

2) Intravenous administration of mercurochrome (40, Eisenstadt, 1931).

3) Intravenous gold sodium thiosulfate and intramuscular bismuth (47, Fister, 1937).

4) Parenteral administration of emetine chloride (102, Henline, 1941).

5) Intramuscular streptomycin in interstitial cystitis with superimposed urinary tract infection (152, Satterthwaite and White, 1948).

6) Oral administration of thiamine chloride (143, Powell, 1949).

7) Supplementary estrogen therapy in post-menopausal females with interstitial cystitis (143, Powell, 1949).

8) Oral administration of potassium iodide (65, Hand, 1949).

9) Parenteral ACTH therapy (182, Weaver and Tyler, 1950).

10) Oral administration of alpha tocopherol (175, Van Duzen and Mustain, 1951).

11) Oral administration of cortisone (73, Hoyt, 1952).

12) Oral administration of banthine (148, Riskind, 1952).

13) Oral administration of an antihistamine, pyribenzamine (160, Simmons and Bunce, 1958).

14) Oral administration of potassium p-amino benzoate (113, McCrea, 1960).

15) Intravenous administration of heparin (183, Weaver, 1963).

16) Oral administration of prednisolone (61, Guerrier et al., 1965).

17) Oral administration of oxyphenbutazone (61, Guerrier et al., 1965).

Miscellaneous

1) External ultraviolet irradiation (69, Higgins, 1930).

2) Immobilization of the bladder by an indwelling catheter (92, Keyes, 1922).

3) Deep X-ray therapy (102, Kreutzmann, 1941).

4) Novocaine infiltration of the erector nerves by the parasacral route (28, Darget, 1944).

5) Dilatation of the bladder with bimanual bladder massage (143, Powell, 1949).

6) Transurethral application of ultraviolet irradiation to the ulcer (19, Caulk and Ewerhardt, 1952).

It has been difficult to evaluate these various modes of therapy since the disease is uncommon; series are small; few studies are controlled in respect to the experimental modality, and the stage of the disease treated. The commonly accepted procedures are discussed below.

Hydraulic overdistention of the bladder, first described by Frontz (99) and popularized by Bumpus (15) has been the primary treatment for all grade lesions, and is commonly used in conjunction with other therapy. Distention has usually to be performed under anesthesia to be effective. Because rupture of the bladder is more common with caudal anesthesia due to nerve blockage and maximal muscle relaxation, general anesthesia is recommended (40). Daily gradual bladder distention or one maximal distention is employed. Franksson reported no significant difference in bladder capacity or in relief of symptoms between these two protocols (52). Bumpus (15) originally reported "gratifying results" in one hundred patients. Franksson (52) in a study of thirty-three patients reported a one-month remission in twelve cases, two to six-month remissions in fourteen cases, and greater than six-month remissions in seven cases.

Fulguration of the ulcer endoscopically with electric current appears to be a useful adjunct in the therapy of interstitial cystitis. The application should be mild to prevent fibrosis and perforation (180,40). The effect is temporary relief of

pain probably due to destruction of C nerve fibres although no data is available to confirm this generally accepted notion.

Instillation of various chemicals which produce a hyperemia of the bladder wall is often used. Silver nitrate in 1:5000 to 1:100 dilution in increasing concentrations is used as an adjunct to bladder distention, although it may be used alone (33). In one hundred and eighty-seven cases treated by distention and silver nitrate instillation, 14% greatly improved, 79% improved, and 7% showed no improvement in respect to frequency, nocturia, and pain (16). The average duration of remission was forty-two days. This is only minimally better than distention alone. Chlorpactin WCS-90, monoxychlorosene, used as a 0.2% solution, in weekly instillations for five weeks is beneficial in decreasing pain and frequency (131, 128). O'Conor (131) reported a 100% therapeutic response initially, and Murnaghan (128) in a two-year follow-up study reported in seventeen patients: 35% greatly improved, 41% improved, and 24% unchanged with respect to pain and frequency. In both studies, 58% of patients required repeated courses of therapy. This is significant since increased fibrosis may be a long term effect of monoxychlorosene (180). Dimethyl sulfoxide, DMSO, is an anti-inflammatory, antiseptic, and analgesic agent, which, when used as an intravesical irrigant has been shown to give symptomatic relief in 75% of cases (171). Further experimental trials have been discontinued by the Federal Drug Administration pending further evaluation of its toxic effects.

The antihistamines, heparin and pyribenzamine, may afford minimal relief. Pyribenzamine 50 mgm three times a day orally gave some relief to four of six patients,

however other therapy was given simultaneously and the study was not conducted as a double-blind trial (159). Heparin, 20,000 units intravenously over twenty-four hours combined with an initial intravesical irrigation with heparin was reported to relieve symptoms within forty-eight hours, but no follow-up is given (183).

Systemic administration of cortisone 100 mgm daily and prednisone 10-20 mgm daily for three weeks has been used with variable results. Hoyt (73) reported no significant effect in four patients, while Guerrier (61) reported relief of pain in nine of eleven patients and decreased frequency in five. Dees (32) noted a decrease in pain and frequency with increased bladder capacity in three of four patients, but all patients relapsed after medication was discontinued. Only Badenoch (2) in 1971 reported significant improvement with steroid therapy. In his series nineteen of twenty-five patients improved with continued daily steroids; of note, all patients were overdistended at the time steroids were begun. Frankson (52) reported a dramatic initial response, but all patients relapsed after the steroids were discontinued. Presently the data suggests that steroid therapy may be beneficial, but must be continued indefinitely to maintain a remission.

Banthine, a parasympatholytic agent, has been reported to decrease frequency and nocturia, without relieving pain in a trial of three patients (143).

Surgical intervention in the treatment of interstitial cystitis is indicated when there is intractable pain, when fibrosis has extended to produce a small contracted bladder necessitating frequent micturition which is unresponsive to conservative therapy, or when ureteral stenosis or reflux causes hydronephrosis.

The surgical treatment of choice for intractable bladder pain is sacral rhizotomy (52,53), if patients are properly selected. Patients with pain in a sacral nerve root distribution respond more favorably than those whose pain is not well localized (53). This can be determined preoperatively by examination and by observing a decrease in pain following infiltration of the sacral nerve roots with local anesthetic agent (52,53). Other authors report an increase in bladder capacity with a decrease in frequency following this procedure (135,126,185).

The surgical treatment of the chronic contracted bladder is some form of cystoplasty or a urinary diversion. Caecocystoplasty, colocystoplasty, or ileocystoplasty have been used (53,23,110). A subtotal cystectomy with removal of all the bladder except the trigone should be performed, and the bowel is anastomosed to the remaining trigonal tissue. This must be done to avoid severe cicatrization at the anastomotic site. Caecocystoplasty is the procedure of choice because of caecal isoperistalsis (53). Frequency is diminished, but pain frequently reoccurs within six months secondary to trigonal spasm (53). Ureterosigmoidostomy has limited usefulness because of the high incidence of ascending infection, hyperchloremic acidosis, osteoporosis, and decreased renal function (147). The ileal conduit has been applied to the treatment of interstitial cystitis. This procedure is more advantageous than ureterosigmoidostomy because there is a low incidence of ascending infection, only a 10% incidence of hyperchloremic acidosis, and in the hands of the usual surgeon will give the most consistent success. Occasionally the surgeon may be obligated to perform a ureterosigmoidostomy if the abdominal stoma

will not be tolerated. Badenoch (2) has collected a series comparing these various procedures.

Procedure	No.	Improved	No change	Worse	Died
Ureterocolic anastomosis	6	4	0	0	2
Cystoplasty	9	5	0	4	0
Ileal conduit	3	3	0	0	0

In patients with intractable and disabling symptoms, urinary diversion is a last resort. Despite all of the methods above some patients are not relieved symptomatically and remain bladder invalids (161).

Part II

An Experimental Study

Introduction

There is only one report of an attempt to induce interstitial cystitis in animals by immunologic methods. Silk in 1970 was unable to produce any lesions in rats or rabbits following a single intramuscular injection of homologous bladder antigen (5 mgm) in complete Freund's adjuvant (158). This amount of crude antigen is small compared to doses of 200-400 mg which have been successfully used to produce lesions in other organs (31,87,29). Multiple injections of antigen will sometimes produce a lesion when single injections of antigen are unsuccessful (31). Heterologous antigens, moreover, are occasionally more effective than homologous antigen in producing a tissue specific auto-immune lesion (28,31,87).

An attempt was made to reproduce the lesions of interstitial cystitis in rats by hyperimmunization with heterologous bladder antigen obtained from rabbits in varying doses and after single and multiple injections accompanied by simultaneous mechanical and bacteriological injury to the bladder.

Animals:

Ten to eleven week old male and female Sprague-Dawley rats weighing between 100 and 150 grams were used. They were segregated by sex and kept five to a cage and fed water and Purina rat pellets ad libitum.

Rabbit Bladder Antigen:

New Zealand albino male rabbits, approximately weighing two kilograms, were sacrificed. Bladders were aseptically removed, debrided of fat and major blood vessels, rinsed with sterile normal saline, dried with sterile gauze, weighed, frozen in dry ice, and ground with mortar and pestle to a granular powder. The ground material was further homogenized in a Duall ground glass tissue homogenizer in sterile normal saline for ten minutes to yield a final concentration of 600 mgm/ml. Dilutions of 200 mgm/ml and 60 mgm/ml were made with sterile normal saline and rehomogenized for two minutes. Homogenates were stored at -20°C in sterile Falcon tubes. On the day of injection, the homogenates were thawed and rehomogenized for two minutes.

Rabbit Skeletal Muscle Antigen and Rabbit Stomach Antigen:

The left rectus femoris muscle and stomachs were also removed aseptically from the same rabbits and treated in the same manner. Final concentrations of the homogenates was 600 mgm/ml.

Preparation of Complete Freund's Adjuvant:

170 cc of Bayol F/Marcol 52 and 30 cc of Arlacel A/mannide mononucleate

(Atlas Chemical Co.) and 1.2 grams of heat-killed, freeze-dried, ground Mycobacteria strains C,D,T,P, and N (Ministry of Agriculture; Surrey, England; courtesy Dr. Byron Waksman) were mixed in a sterile bottle by agitation. This complete Freund's adjuvant was stored at -20°C. The final concentration contained 6 mgm/ml of Mycobacteria.

Preparation of Antigen-Adjuvant Mixtures:

Fresh mixtures were prepared on each day of injection. Tissue homogenates and a sterile normal saline control were added to complete Freund's adjuvant in a 1:1 ratio (by volume), emulsified with a syringe, and then mixed with a Thomas teflon homogenizer for five minutes. Mixtures were tested for emulsification by the absence of dispersal when droplets of the mixture were placed on a water surface. Final concentrations were: Rabbit Bladder Antigen: 300 mgm/ml, 100 mgm/ml, and 30 mgm/ml; Rabbit Skeletal Muscle Antigen: 300 mgm/ml; and Rabbit Stomach Antigen: 300 mgm/ml.

Experimental Design:

All rats were anesthetized with diethyl ether prior to injection according to the following protocols.

Protocol "A":

Sixty rats were divided into seven sex equal groups, and were injected with 1.0 ml of an antigen adjuvant mixture, 0.5 cc distributed among 3 footpads

excluding the left hind side, and 0.1 cc in each of five subcutaneous sites in the right flank as follows:

Group	No. Animals	Antigen/Dose
1	12	Bladder 300 mgm/ml
2	12	Bladder 100 mgm/ml
3	12	Bladder 30 mgm/ml
4	8	Muscle 300 mgm/ml
5	8	Stomach 300 mgm/ml
6	8	Saline Control
7	8	No injection

On the tenth, fourteenth, twenty-first, and twenty-eighth day after the injections, one-fourth of each original group was sacrificed.

Protocol "B":

Sixty rats were divided into seven groups identical to those in Protocol "A" and given the same initial injection. At two-week intervals all animals were re-injected with 0.5 cc of the same antigen-adjuvant mixture in the right flank, in five subcutaneous sites (0.1 cc per site), for a maximum of four re-injections. On the twenty-eighth, forty-second, fifty-sixth, and seventieth day after the original injection, one-fourth of each original group was sacrificed.

Protocol "C":

Four rats, on the day following the fourth re-injection (as in Protocol "B") were operated upon to induce bladder injury.

Rat	Antigen	Dose
1	Bladder	300 mgm/ml
2	Bladder	100 mgm/ml
3	Bladder	30 mgm/ml
4	Saline Control	

After induction of anesthesia with Nembutal 30 mgm/ml intraperitoneally, the suprapubic area was shaved and cleansed with benzalkonium and 95% ethyl alcohol. A vertical midline suprapubic incision was made to expose the bladder. The dome of the bladder was clamped with a small hemostat for three minutes and the abdomen was closed. The animals were sacrificed on the fourteenth postoperative day.

Protocol "D":

A group of four rats identical to those in Protocol "C" were operated upon fourteen days after the fourth re-injection. They were prepared and anesthetized in the same manner. A 3 mm round glass bead was inserted into the bladder through a small cystotomy, the bladder was closed with 6.0 catgut. A 0.1 ml of 10^5 cells/ml of E. coli strain ECY (courtesy L. Freedman) was then injected into the bladder with a #27g needle 5 mm from the incision site. The rats were sacrificed on the fourteenth postoperative day.

Method of Sacrifice:

Animals were sacrificed with ether. The viscera were examined macroscopically after the thorax and abdomen were exposed. Sections of the left rectus femoris muscle, stomach, urinary bladder, heart, lung, kidney, liver, spleen,

and left testis or left ovary were removed and fixed in 10% neutral formalin. Histologic sections of each bladder were made and stained with hematoxylin and eosin.

Results

Protocol "A"

In the gross examination there was no difference in the appearance between the control and the experimental bladders or any other organ. Residual of pleural fibrosis were found in occasional animals from each group. In microscopic section, there was no difference with respect to the bladder histology when examined for edema, cellular infiltration, or fibrosis.

Protocol "B"

The results in this study were similar to that found in "A".

Protocol "C"

In the gross examination, there was minimal thickening of the bladder wall in the area of injury. In microscopic section, all bladders appeared to have a minimal increase in fibrosis in this injured area. There was neither cellular infiltrate nor edema. There was no difference between the experimental animals and the controls.

Protocol "D"

In the gross examination, all animals showed thickening of the bladder wall at the suture site with minimal peritoneal adhesion. The microscopic examination findings were similar to those in Protocol "C," without evidence of cystitis or infection.

Interstitial cystitis has many characteristics of an auto-immune disease: the chronic clinical course; the association with collagen diseases; the age and sex distribution; the histopathology; an apparent response in some patients to steroid and antihistamine therapy; and the presence of antinuclear factor and anti-bladder antibodies in some patients (157,2,159,183,60,158). In addition, Waksman states that, "any disease of unknown etiology in which infection, tumor, and deficiency state have been ruled out, may be suspicious of having an immunologic basis (178)."

There are two broad categories of auto-immune disease: tissue specific and non-tissue specific (178). The latter are characterized by the following: antibodies that react widely with different tissues of the same and other species, e.g., anti-nuclear factor; antigens that are accessible to the lymphatic circulation and available to immunologically competent cells, e.g., nucleoprotein; an increased incidence of antibodies that react to various tissues, e.g., antithyroid antibodies; a familial pattern; antibodies that react with antigens to which normal individuals are tolerant, e.g., anti-DNA; and a lesion which is difficult to produce in experimental animals (178). Two examples of non-specific auto-immune disease are systemic lupus erytematosus and rheumatoid arthritis. These diseases are thought to be caused by an immunologic abnormality that allows the formation of auto-antibodies and auto-sensitized lymphocytes to react against unaltered, non-foreign antigen. In summary, there is a "central" failure to recognize "own" antigens (178), to which tolerance is normally developed.

The tissue specific diseases have different characteristics: auto-antibodies that react(s) with (a) component(s) from a single organ from many species; the relevant antigens may be separated from lymphatic contact, e.g., lens capsular protein; tolerance to these antigens usually is not developed in the host; and experimentally the lesions can be produced in animals by the injection of the tissue specific antigen incorporated in complete Freund's adjuvant (177,178). Hashimoto's thyroiditis, post-rabies vaccination encephalomyelitis, and idiopathic Addison's disease are thought to represent this category of auto-immune disease. The lesion is thought to occur from an humoral and/or cellular response to the non-tolerant antigen, and is believed to be initiated in the following ways: unaltered endogenous antigen, previously "hidden" from the lymphatic system gains entry to the latter inducing an immunologic response; antigen to which the host is tolerant becomes altered, e.g. by infarction, initiating an immunologic response which cross reacts with the original antigen; exogenous antigen induces an immunologic response which cross reacts with endogenous antigen, e.g., rheumatic fever; or a "forbidden clone" produces antibodies and/or lymphocytes that react with a tolerant or nontolerant antigen as in paroxysmal nocturnal hemoglobinuria.

Interstitial cystitis does not appear, however, to belong to either group exclusively. The disease does not represent a non-tissue specific disease totally. Although 85% of patients have been reported to have antinuclear factor in greater than 1:10 titer (84,132), patients do not have an increased incidence of other auto-antibodies when compared to matched controls (84). Although three cases have

been reported with the LE phenomenon (60,157), this has not been a consistent finding (84). These findings are probably only coincidental, rather than providing evidence that interstitial cystitis is a variant of lupus.

Interstitial cystitis does not represent tissue specific disease totally either. In only nine of Silk's twenty patients were anti-bladder antibodies demonstrated (158), a finding not confirmed by Jokinen (84). Furthermore, Gordon was able to demonstrate such antibodies in patients with a variety of bladder disorders (60). Gordon reported one patient whose lymphocytes underwent blastogenesis as measured by radioactive thymidine uptake when exposed to bladder antigen, but this patient also demonstrated the LE phenomenon, and it is not clear to which disease this phenomenon should be attributed to since no other patients were tested. Patients with tissue specific auto-immune diseases are reported to have a higher incidence of auto-antibodies to other organs, but this is not characteristic of interstitial cystitis (84). McGuire and Lytton in a clinical report found histopathologic changes of round cell infiltration and fibrosis in the submucosa of colonic tissue which had been used for a colocystoplasty as treatment in a case of chronic interstitial cystitis. This lesion was undistinguishable from the bladder lesion in interstitial cystitis. Finally, Silk was unable to produce this lesion in rats or rabbits experimentally by the injection of homologous antigen (158). The present investigation also failed to produce any bladder lesions following hyperimmunization with heterologous antigen in rats. There are several possible explanations which could account for this failure:

1) Animals were not sensitized because:

   a) bladder protein is a poor antigen (this, however, is probably not a factor since when guinea pigs were skin tested with bladder protein after hyperimmunization with bladder antigen in a complete Freund's adjuvant, delayed hypersensitivity occurred.)

   b) antigen doses were inappropriate

   c) the preparation of the protein destroyed its antigenic properties

   d) the animals were or became tolerant to the antigen

2) Animals were sensitized, but

   a) rabbit bladder antigen does not cross react with rat bladder

   b) anti-bladder antibody "blocked" cytotoxic lymphocytes

3) Rats are not subject to auto-immune disease of the bladder

Only further investigation will clarify these points.

Chronic interstitial cystitis, if indeed is an auto-immune disease, would be considered to have some characteristics of both types of auto-immune disease as suggested by Jokinen (84). Presently the data suggests that immunologic mechanisms are not the cause of interstitial cystitis, but that these patients may exhibit immunochemical abnormalities.

Further investigation must be pursued both experimentally and clinically if the etiology is to be more clearly defined. Testing for the presence of the LE phenomenon, antinuclear factor, complement level, circulating anti-bladder antibodies, lymphocyte toxicity to bladder cells, and lymphocyte blastogenesis upon

exposure to bladder protein could be evaluated in patients with clearly defined interstitial cystitis and might be of help in determining whether in fact the condition should be considered a true auto-immune disease.

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